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Antibiotic Prophylaxis and Therapy of Airborne Tularemia

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INTRODUCTION

Streptomycin was the first effective antibiotic for the therapy of tularemia, and remains the drug of choice (1, 14, 21). Alternatives are needed, however, because of (i) the possibility of infection by streptomycin-resistant *Francisella tularensis* (11), (ii) the need for injection of streptomycin with the attendant inconvenience and discomfort, and (iii) the toxicity of streptomycin. Of the many other antibiotics active against *F. tularensis*, the best evaluated and most frequently used are the tetracyclines and chloramphenicol (2, 9, 11, 12, 20). (Because chloramphenicol offers no advantages over the tetracyclines in the treatment of tularemia and has significant toxicity, only the tetracyclines will be considered hereafter except in reviewing earlier work.) Patients with acute tularemia respond well to therapy with either streptomycin or tetracycline; symptoms rapidly remit, and defervescence is prompt (Fig. 1). The late consequences of treatment with the two antibiotics differ, however. Relapses rarely follow exhibition of reasonable doses of streptomycin but occur frequently after therapy with conventional regimens of tetracycline (2, 11). Such relapses result from the persistence of bacteria in the tissues, not the emergence of tetracycline-resistant organisms; retreatment with tetracycline is effective (Fig. 1).

In addition to their use in the management of tularemia, antibiotics may be employed for prophylaxis, used here to mean treatment instituted during the incubation period to prevent illness. Results have been similar to those achieved in the therapy of acute disease: streptomycin prevents illness, but broad-spectrum drugs merely delay disease. McCrumb et al. (9), for example, consistently protected volunteers by administration of streptomycin for 5 days after intradermal inoculation with *F. tularensis*, whereas only two of five volunteers were protected from tularemia by 5 days of prophylactic treatment with chloramphenicol.

Comparison of their actions against *F. tularensis* in vitro may help to explain the difference in effectiveness of streptomycin and tetracycline in both the prophylaxis and therapy of tularemia. Streptomycin is bactericidal in vitro, and may eradicate the organisms without the intervention of host mechanisms. Tetracycline, even in high concentration, merely suppresses multiplication; organisms persist in the tissues until destroyed by host defenses. *F. tularensis*, like other intracellular pathogens (5,17), is cleared from the cells slowly even when multiplication is prevented, e.g., by a bacteriostatic antibiotic. The relative inefficiency of host defense against *F. tularensis* is a crucial factor in determining the effectiveness of prophylaxis and therapy of tularemia with bacteriostatic agents. In the Conference on Airborne Infection held in 1960, McCrumb cited the imperfect results achieved with bacteriostatic drugs and suggested that either prolonged or intermittent treatment might be required if they were to be completely effective (10). The success of such regimens in other intracellular infections, e.g., scrub typhus (8, 16) and Q fever (18, 19), prompted the present studies of tetracycline prophylaxis and therapy of experimental airborne tularemia in *Macaca mulatta* and man.

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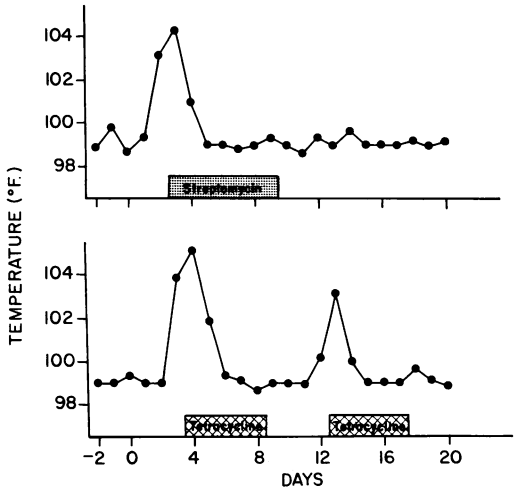

FIG. 1. *Therapy of experimental human airborne tularemia with streptomycin and with tetracycline. Doses were: streptomycin, 1 g twice daily; and tetracycline, 0.5 g four times daily.*

TETRACYCLINE PROPHYLAXIS

Simian Tularemia

Monkeys were exposed to aerosols of *F. tularensis* SCHU-S4 generated in a modified Henderson apparatus (3, 4, 7). [Healthy young adult *M. mulatta*, weighing 3 to 6 kg, were obtained from the Animal Farm, Fort Detrick, Md. Pre-exposure sera did not contain *F. tularensis* agglutinins. Cultures of *F. tularensis* were kindly supplied by H. T. Eigelsbach. They were grown in modified casein hydrolysate medium (Mills et al., Bacteriol. Proc., p. 37, 1949) for 16 hr with continuous shaking at 37 C, and were stored at 4 C until used. The SCHU-S4 strain is sensitive to streptomycin.] The average inhaled dose was 10,000 organisms, a quantity regularly resulting in an acute fatal illness after a short incubation period (Fig. 2). [In addition to twice daily examination and thermometry, serum C-reactive protein was determined and a chest X ray was obtained at weekly intervals (or more frequently upon request of the attending veterinarian). Fever (rectal temperature > 40 C) was the principal criterion of illness.] The results of five schedules of tetracycline prophylaxis are shown in Table 1. In all schedules, the initial dose of drug was given 24 hr after exposure, and prophylactic treatment lasted for 13 days. Illness was suppressed in 10 of the 11 animals receiving the antibiotic at 24- or 36-hr intervals; an unrelated, intercurrent illness cannot be excluded in the one exception. When the interval between doses was increased beyond 36 hr, however, the animals experienced one or more febrile episodes during the treatment period. Because tetracycline administered at 48-hr intervals failed to suppress disease, a different sort of interrupted schedule was tried, i.e., 3-day treatment periods alternating with 2-day periods without drug. Four of the six monkeys were ill during the prophylactic period. Frequent administration of tetracycline, therefore, appeared necessary to limit multiplication of *F. tularensis* so that the infection remained subclinical during the treatment period.

After completion of all of the prophylactic regimens, most of the monkeys became ill (Table 1). Clearly, *F. tularensis* had remained viable in the host tissues throughout the period (13 days) of antibiotic administration. That the duration of persistence could be quite prolonged was demonstrated in another group of monkeys which received tetracycline daily for 6 weeks. Monkeys tolerated prolonged tetracycline treatment well, i.e., weight was maintained and no illnesses

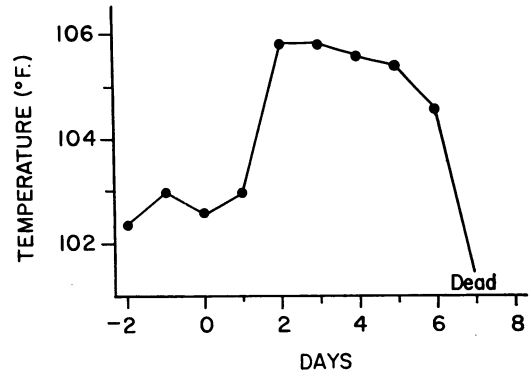

FIG. 2. *Course of fever in experimental simian airborne tularemia.*

TABLE 1. *Tetracycline prophylaxis of airborne tularemia in Macaca mulatta*[a]

Dosage interval	No. of doses	No. of monkeys	No. ill during treatment	No. ill after treatment	No. of deaths
hr					
24	13	5	1	5	0
36	9	6	0	4	1
48	7	6	6	6	1
72	5	6	6	6	0
Intermittent[b]	9	6	4	2	0

[a] Each animal received 200 mg of tetracycline intragastrically beginning on day 1 and continued over a period of 13 days. Six of six untreated animals developed fatal tularemia.

[b] Days 1 to 3, 6 to 8, 11 to 13.

attributable to the drug or to "superinfection" were detected. All remained well throughout the treatment period, but two of the six animals developed acute tularemia within 6 days of the last dose of drug. Because rigid precautions were taken to prevent re-exposure to *F. tularensis*, e.g., cross-infection, accidental laboratory aerosol, etc. (6, 7), these illnesses are believed to have resulted from organisms which were not eliminated during the 42 days of tetracycline treatment.

Even with treatment once a day, tissue levels of tetracycline undoubtedly fluctuated considerably, and, when levels were lowest, the organisms might have undergone several cycles of multiplication without yielding a bacterial mass sufficient to produce illness. This seemed unlikely, because agglutinins did not develop in monkeys who remained well during the course of daily prophylaxis (Fig. 3). When these animals became ill after cessation of treatment (see above), agglutinins promptly appeared. Agglutinin titers increased early in monkeys receiving prophylaxis which failed to suppress illness.

Although prophylactic treatment of tularemia with tetracycline failed to prevent illness, it reduced the severity of the disease. Whereas all of the six untreated monkeys died of tularemia, only two of those in the several prophylaxis groups expired within 70 days of exposure, the duration of observation (Table 1).

Because the timing of the institution of treatment may have important bearing on the effectiveness of prophylaxis of intracellular infection [e.g., tetracycline prophylaxis of Q fever merely delays illness if instituted early but is preventative when begun during the last half of the incubation period (18, 19)], initiation of prophylactic treatment was delayed until 60 hr after exposure to *F. tularensis* in one group of monkeys. The results were no better than those obtained with earlier treatment (Table 2). Further delay in initiating prophylaxis was not feasible, because most monkeys became ill between 60 and 72 hr after exposure.

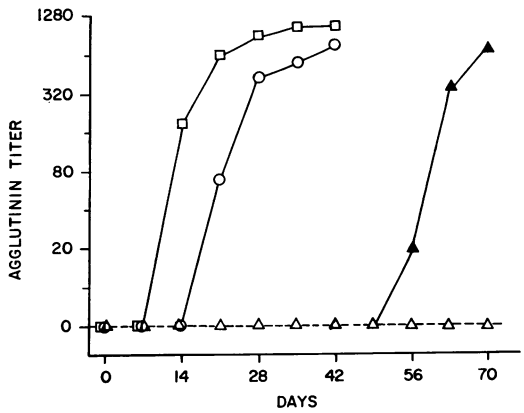

FIG. 3. *Mean Francisella tularensis agglutinin titers of Macaca mulatta receiving tetracycline prophylaxis for airborne tularemia. Symbols:* □ *drug every 48 hr, 6 doses;* ○ *drug daily, 13 doses;* △, *drug daily, 42 doses, animals remaining well;* ▲, *drug daily, 42 doses, animals becoming ill after treatment.*

TABLE 2. *Tetracycline prophylaxis of airborne tularemia in Macaca mulatta—Delayed institution of treatment*[a]

Treatment instituted (hr postexposure)	No. of monkeys	No. ill during treatment	No. ill after treatment	No. of deaths
24	5	1	5	0
60	6	1	6	2

[a] Each animal received 200 mg intragastrically once daily for 13 doses.

Human Tularemia

The failure of prolonged tetracycline prophyllaxis to prevent simian airborne tularemia results from the limited defenses of *M. mulatta* against *F. tularensis*. Although man is quite susceptible to infection with airborne *F. tularensis*, he has better defense mechanisms than *M. mulatta*; e.g., the human respiratory infectious dose is about three times that of monkeys (15), and untreated airborne tularemia has a mortality of less than 50% in man (13) but is usually fatal in monkeys. It seemed likely, therefore, that prophylactic regimens of tetracycline which were only partially successful in monkeys might succeed in man.

The results of trials in volunteers who inhaled 25,000 *F. tularensis* SCHU-S4 confirmed the prediction (Table 3). [Healthy young Seventh Day Adventist soldiers participated on a voluntary basis; they were informed of the nature of the studies prior to volunteering (Army Regulation 70-25, Use of volunteers as subjects of research). The men were observed closely in the hospital before and after exposure. Sera obtained prior to participation did not contain *F. tularensis* agglutinins. The volunteers were examined at least twice daily, and their rectal temperature was recorded every 6 hr. Blood count, erythrocyte sedimentation rate, and serum C-reactive protein were determined and a chest X ray was obtained weekly (more often during periods of illness). Fever (rectal temperature >37.8 C), unassociated with signs of a disease other than tularemia, was the principal criterion of illness.

TABLE 3. *Tetracycline prophylaxis of human airborne tularemia (treatment instituted 24 hr after exposure)*

Daily dose[a]	Frequency	Duration	No. of subjects	No. ill during treatment	No. ill after treatment
g		*days*			
1	Daily	15	10	0	2
1	Daily	28	8	0	0
2	Daily	14	8	0	0
1	Every 2nd day	19	8	2	8

[a] Divided into morning and evening doses.

Volunteers who developed disease after completion of an experimental schedule of tetracycline were promptly treated with streptomycin, 1 g each 12 hr for 14 doses. All recovered quickly without complications or sequelae. Aerosols of *F. tularensis* were created in a modified Henderson apparatus (3, 4). The men inhaled through the nose and exhaled through the mouth.] All control subjects developed acute tularemia between 2 and 7 days after exposure. (These men participated in studies of therapy; see below). Administration of 1 g of tetracycline each day, beginning 24 hr after exposure, completely suppressed illness during the treatment period, but when treatment was stopped after 15 days, 2 of 10 volunteers developed acute tularemia. Extension of treatment to 28 days prevented illness. Complete protection was also achieved by administration of 2 g of tetracycline daily, even though treatment was terminated after 14 days. Intermittent drug administration, i.e., every other day, failed to protect the volunteers. The pattern of agglutinin response was consistent with the clinical effectiveness of prophylactic therapy, i.e., titers were high (1:1,280) in subjects after overt illness but negative or low (1:80 or less) in the men who remained free from disease.

In contrast to the results in *M. mulatta*, the human studies showed that satisfactory prophylaxis of airborne tularemia could be achieved with tetracycline, the simplest and shortest regimen being 2 g of drug daily for 14 days. With this schedule, disease was completely suppressed both during and after the treatment period; *F. tularensis* agglutinins either did not appear or developed only in low titer.

TETRACYCLINE THERAPY

The initial objective in the therapy of acute tularemia is the rapid relief of clinical manifestations, an objective readily accomplished with bacteriostatic drugs (see above). Thereafter, the problem is the same as that in prophylaxis—the suppression of multiplication for sufficient time for host mechanisms to eradicate the microorganisms. The major difference, then, in the two situations is the extent of microbial multiplication, and supposedly the degree of stimulation of defense mechanisms, prior to initiation of treatment. Therefore, after control of clinical illness, therapeutic regimens similar to those found effective in prophylaxis should result in a negligible relapse rate, even if therapy is instituted early in the course of disease.

Volunteers exposed to 25,000 airborne *F. tularensis* (see above) became acutely ill after a mean incubation period of 3 days (range of 2 to 7 days). The onset of illness was gradual in 15% of subjects, and a biphasic course was occasionally observed. Treatment was instituted early, within 48 hr of initial signs of illness in 85% of the men, and in no case later than the 5th day after initial signs. Large doses of tetracycline were administered during the first 24 hr, i.e. 1 g every 6 hr, to insure high initial blood levels, and the daily maintenance quantity was administered thereafter in four equal doses.

During the initial phases of evaluation of tetracycline therapy, intermittent treatment schedules were examined. Therapy consisting of three five-day courses of tetracycline (0.5 g every 6 hr) separated by 3 days without drug was efficacious (Fig. 4); the patients responded rapidly and remained well thereafter. These results led

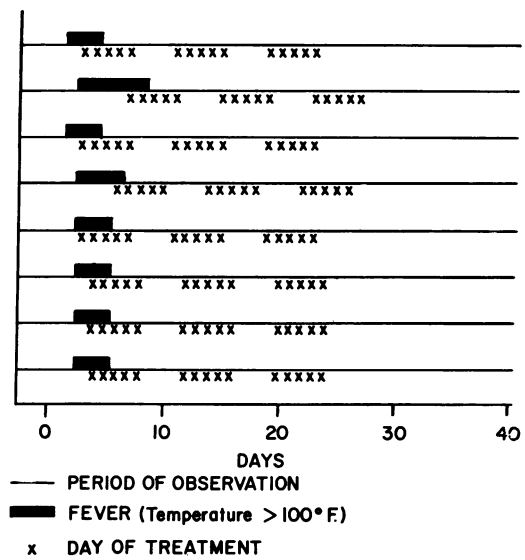

FIG. 4. *Interrupted tetracycline therapy of human airborne tularemia.*

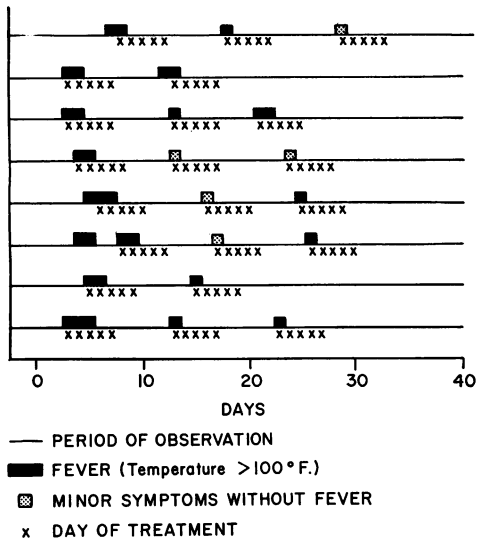

FIG. 5. *Interrupted tetracycline therapy of human airborne tularemia.*

to an attempt to reduce the number of treatment periods. After the initial 5 days of therapy, no additional drug was given to another group of volunteers until ordered by the ward physician, who was instructed to institute treatment at the first sign, no matter how equivocal, of a recurrence. The results were unsatisfactory (Fig. 5). In most instances, the recurrences were so rapid in onset that the men were disabled by the time treatment was effectively instituted; i.e., the time between recognition of possible recurrence and achievement of effective levels of drug in the patient exceeded the time required for the illness to progress from well-being to disability. Moreover, three courses of treatment were administered in 6 of the 8 subjects. It seemed, therefore, that there was little likelihood of developing effective interrupted treatment schedules either employing substantially less drug or of shorter duration than that originally evaluated. Later studies (see below) indicated that continuous tetracycline therapy with similar quantities of drug was equally effective; interrupted therapy, therefore, did not offer any advantage over the simpler continuous treatment schedule.

Prompt clinical improvement was achieved with the continuous therapeutic regimens listed in Table 4. Treatment with 22 g of tetracycline in 10 days resulted in a high incidence of relapse. The same daily dose continued through 15 days was not, however, followed by relapse in any of the 20 patients, 12 infected with the SCHU-S4 strain and 8 infected with the SCHU-S5 strain. The SCHU-S5 strain differs from SCHU-S4 strain only in resistance to streptomycin, SCHU-S5 resisting more than 1,000 μg/ml. When the daily dose was halved, two of eight men had a relapse after 15 days of therapy.

As predicted, the simplest and most successful tetracycline regimen for prophylaxis was very similar to the best therapeutic regimen, i.e., 1 g of tetracycline twice daily for 14 days compared with 4 g of tetracycline the 1st day followed by 0.5 g four times daily for 14 additional days. From a practical standpoint, it would be desirable to have a single schedule of tetracycline administration for both prophylaxis and therapy of airborne tularemia. Therefore, six volunteers with acute illness were treated exactly according to the schedule found successful for prophylaxis; all recovered rapidly and remained well. Thus, a simple schedule of tetracycline treatment was effective in both prophylaxis and therapy of human airborne tularemia; that schedule was 1 g of tetracycline twice daily for 14 days. Because this treatment schedule was suitable for infections induced by exposure to a large number of organisms, the regimen should be satisfactory over the entire range of exposure encountered either in nature or in laboratory accident.

OTHER ANTIBIOTICS

For infection with streptomycin-sensitive *F. tularensis*, the clinician has a choice of effective antibiotics, particularly streptomycin and tetracycline. In cases of infection by streptomycin-resistant organisms, effective alternatives to tetracycline are needed. Therefore, a number of antibiotics active against *F. tularensis* SCHU-S5 (streptomycin-resistant) in vitro have been evaluated in the therapy of airborne infection of monkeys with the SCHU-S5 strain (Table 5). The inhaled dose was 10,000 organisms; 12 control monkeys became ill within 72 hr and died between the 7th and 15th day after exposure. Therapy was started early, i.e., after 12 hr with a

TABLE 4. *Tetracycline therapy of human airborne tularemia*

Daily dose[a]	Days of therapy	No. of subjects	No. with relapse
g			
2	10	11	5
2	15	20[b]	0
1	15	8	2

[a] All men received 4 g of drug the 1st day of therapy. Daily dose was given at 6-hr intervals.

[b] Twelve men infected with the SCHU-S4 strain and eight with the SCHU-S5 strain of *Francisella tularensis*.

TABLE 5. *Antibiotic therapy of Macaca mulatta infected with Francisella tularensis SCHU-S5*

Antibiotic	Daily dose[a]	No. of monkeys	No. with slow response[b]	No. with relapse
	mg			
Tetracycline	225	8	1	8
Kanamycin	90	8	2	0
Novobiocin	135	6	1	5
Gentamicin	9	8	8	3

[a] Divided into three doses. Therapy was continued for 7 days or until the animal was afebrile for 72 hr, whichever was longer.

[b] An animal was classified as having a slow response if more than 72 hr of treatment were required before it became afebrile.

temperature >40 C or a single temperature of 41 C or greater. Tetracycline treatment resulted in rapid response, but, as expected, relapses followed this short course (*see* Table 5). Kanamycin, which was bactericidal in vitro, was bactericidal in vivo as well, and effected cure, albeit the initial response was somewhat slow in two monkeys. Novobiocin (Eigelsbach, Herring, and Halstead, Bacteriol. Proc., p. 69, 1957) gave results similar to those obtained with tetracycline. Although gentamicin was quite active against *F. tularensis* SCHU-S5 in vitro, therapy with it was disappointing. All monkeys responded, but only slowly; three of the eight had a relapse.

These results suggest that novobiocin may be employed in the therapy of human tularemia, but that prolonged courses, such as those found necessary with other bacteriostatic drugs, are likely to be necessary if therapy is to be completely successful. Although the bactericidal drug kanamycin was highly effective, its toxicity is such that it cannot be recommended for primary treatment. It may, however, be of value as a "backstop" in chronic, recurring infections and as an alternative to the broad-spectrum drugs in the management of infections by streptomycin-resistant organisms.

SUMMARY

Unlike streptomycin, tetracyline and the other broad-spectrum antibiotics do not kill susceptible *F. tularensis* in vitro or in vivo. The broad-spectrum drugs owe their effectiveness to their bacteriostatic action; they check multiplication of the invading organisms until host defense mechanisms can eliminate the bacteria. Elimination of *F. tularensis* within cells proceeds slowly, and organisms may persist for many days in man (and many weeks in monkeys) during tetracycline treatment. The results of the present studies of tetracycline treatment indicate that infection with *F. tularensis* can be eradicated through bacteriostatic antibiotic therapy provided (i) that the antibiotic is administered in amounts sufficient to obtain continuous suppression of growth of intracellular organisms, and (ii) that the regimen is maintained for a sufficient period of time. These objectives have been met by a regimen of 2 g of tetracycline daily for 14 days. This regimen may be employed both for prophylaxis and for therapy of human airborne tularemia.

ACKNOWLEDGMENTS

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Discussion

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The elegant work of Dr. Sawyer and his colleagues presents data which are of considerable importance, not only to those dealing with tularemia and related diseases, but also to many investigators who are interested in the general principles of antibiotic therapy and prophylaxis. This discussion is based on a general perspective, with emphasis on the prophylactic aspects.

All chemotherapeutic activity must be viewed in terms of the therapeutic ratio concept. Since there is rarely an assurance in natural situations that any given individual upon exposure will develop a clinical illness, the therapeutic ratio in the prophylactic situation has to be expressed in terms of group risk, group results, and group toxicity. Thus, if only one-half of an exposed population is destined to become ill and the prophylactic regimen gives no better end results than the treatment of half the group of subjects who actually become ill, the toxicity is doubled for the group as a whole and the results are no better than those of therapy; hence, the therapeutic ratio is less favorable. Since the accentuation of toxicity is the most marked effect of prophylaxis, prophylaxis is usually attempted with the least toxic drugs or with a reduced dose. In addition, because it is often not possible to determine with accuracy the expected infection rate in the natural situation, it has been more difficult to measure prophylactic than therapeutic benefits. Clearly, the animal and volunteer studies of Sawyer meet the problem of evaluation well and thus provide important insight. Unfortunately, even the results of treatment of a random sample of an exposed population in a semiclosed situation, when the infection rate is unpredictable, may be difficult to interpret, since the treatment of some members of the group may influence the infection rate among the untreated.

The most important principle illustrated by these data is the primary importance of the host defense mechanisms. The superior results in man as compared with monkeys correlates well with the higher spontaneous recovery rates among the former. It is possible that much of what has been demonstrated is interpretable in terms of the